Time Trends in Lung Cancer Mortality Among Nonsmokers and a Note on Passive Smoking [1]

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ABSTRACT—Lung cancer mortality rates were computed for nonsmokers in the American Cancer Society's prospective study for three 4-year periods from 1960 to 1972 and in the Dorn study of veterans for three 5-year periods from 1954 to 1969. There was no evidence of any trend in these rates by 5-year age groups or for the total groups. No time trend was observed in nonsmokers for cancers of other selected sites except for a decrease in cancer of the uterus. Compared to nonsmoking women married to nonsmoking husbands, nonsmokers married to smoking husbands showed very little, if any, increased risk of lung cancer.—JNCI 1981; 66:1061-1066.

Mortality rates from lung cancer in men in the United States have been rising steadily since 1930 (the first year these cancers were classified separately) and in women since the mid-1960's. It has generally been accepted that the major reason for the increase has been the cigarette smoking patterns which began in young men around World War I and in young women in the 1930's and 1940's. A large body of evidence from epidemiologic and pathologic studies on smokers confirms this conclusion (*1*). A recent estimate of the percentage of cancers attributable to smoking in men was 34.5% for total cancers and 82.8% for lung cancer. In women the comparable percentages were 5.4 and 43.1% (*2*). This analysis was based on data from the large epidemiologic study of the ACS and covered the period 1967-71. It was based on a number of assumptions that would give slightly different figures if the smoking distributions in the study population differed from those of the general population or if smoking distributions changed in the late 1970's compared to the late 1960's (as they indeed have in women).

There has been a suggestion, however, that the lung cancer trend in nonsmokers has also increased in the United States over the years. Enstrom (*3*) stated that "a more complete understanding of lung cancer etiology is needed." This analysis indicated a large relative increase in lung cancer mortality in nonsmokers in both white men and white women between 1914 and 1975 on the basis of an interpretation of data in samples of national mortality statistics and several epidemiologic studies in different periods of time (*3*). Enstrom recognized that most of the increase occurred between a 1914 survey of death registration areas in 24 states and national mortality statistics reported in 1935 and that most of that increase was probably attributable to incompleteness of reporting lung cancer and to changes in diagnostic criteria.

Nevertheless, the possibility exists that lung cancer is increasing in nonsmokers who have had increasing exposure to other factors—occupational exposures, general air pollution, and perhaps even to passive smoking (inhaling the smoke from smokers). Even if these factors were related to the alleged increase in lung cancer, they could have had only minimal effect on the upward trend for lung cancer in men, since the mortality rates among smokers and nonsmokers differ so greatly. Moreover, in the last 50 years and until recently, most men had a history of cigarette smoking. Among women lung cancer rates remained low up to about 1960. Since then, there has been a threefold increase in rates attributable in large part to the changes in smoking patterns among women during the preceding two or three decades.

In this paper, information is provided on trends for lung cancer (and cancers of several other sites) in nonsmokers over a 12-year period (1960-72) from data in the prospective study of the ACS. In addition, data for nonsmokers from the Dorn study of veterans for the years 1955-69 are given. While such data do not provide evidence over a very long time span, they are based on the two largest prospective studies in the United States and cover a 17½-year period from 1955 to 1972.

MATERIALS AND METHODS

Procedures in the collection of data in the prospective study of the ACS have been presented in a number of publications (*4-6*). There were 94,000 male and 375,000 female nonsmokers at the start of the study. In the ACS study, a "nonsmoker" is one who reported he or she had never smoked or smoked only occasionally but had never smoked regularly. Classification was made as of the start of the study, and very few nonsmokers reported that they started to smoke on any of four later questionnaires.

Enrollment of subjects in the ACS study began in October 1959 and extended through March 1960. Follow-up was complete for 98.4% of all subjects through June 1971 and 92.8% complete for the 12th year of the study. Deaths were reported by the ACS volunteers, and death certificates were obtained from state health de-

Abbreviation used: ACS = American Cancer Society.

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partments. Mortality data for this analysis begin with observation starting on July 1, 1960. Data are presented for three 4-year periods: period 1, July 1, 1960, through June 30, 1964; period 2, July 1, 1964, through June 30, 1968; and period 3, July 1, 1968, through June 30, 1972. Person-years of observation in nonsmokers and deaths at single years of attained ages 35–89 years were computed and combined by 5-year attained age groups.

In the Dorn study of veterans, questionnaires were mailed starting in January 1954 to 293,000 veterans holding U.S. Government life insurance. About 65% of the questionnaires were received over a period of several months. In January 1957 a second questionnaire was mailed to those not responding to the first mailing and the replies raised the total to 85% (7). About 54,000 of those who replied were nonsmokers. The same classification of nonsmokers was used in this study as was used for the ACS study. Person-years of observation and mortality by single years of attained age were computed starting with January 1, 1955, for the responders to the first mailing and starting with January 1, 1958, for the responders to the second mailing. Death certificates were supplied to the Veterans' Administration in support of insurance claims through 1962. For the period 1962–69, death certificates were obtained through field work at health departments by ACS personnel (*8*).

Death rates by 5-year age groups were adjusted to the distribution of the stationary population ($_nL_x$) of white men and white women of ages 35 years and over in the abridged life tables for the U.S. population in 1965 (*9*). Differences in death rates for periods 1 and 2 and periods 1 and 3 were tested for significance at the $P<0.05$ level by the Mantel-Haenszel procedure (*10*).

RESULTS

Time Trends in Lung Cancer Mortality Among Nonsmokers

Table 1 shows the 5-year attained age death rates for lung cancer among nonsmokers in three periods of time. The table includes men and women in the ACS study and men in the Dorn study of veterans. There were 195 deaths from lung cancer among male nonsmokers and 564 deaths from lung cancer among female nonsmokers in the ACS study during the 12-year period. There were 168 deaths from lung cancer among nonsmokers in the 15-year period in the Dorn study of veterans. Some of the rates computed for 5-

TABLE 1.—*Death rates from lung cancer per 100,000 person-years among nonsmokers, ages 35–89 years, by time period: ACS prospective study and the Dorn study of veterans*

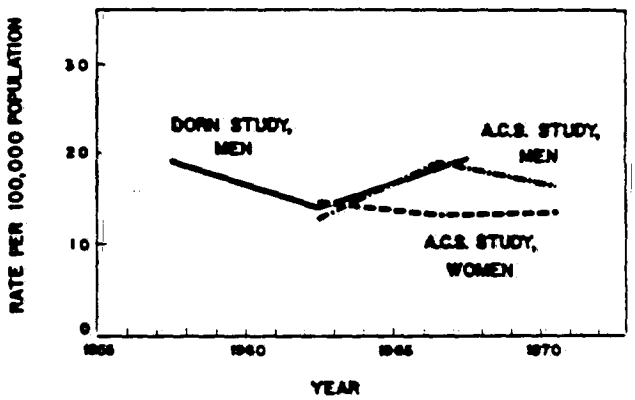
Attained age group, yr[a]	ACS prospective study[b]			Dorn's study of veterans[b]		
	Period 1: July 1960–June 1964	Period 2: July 1964–June 1968	Period 3: July 1968–June 1972	Period 1: Jan. 1955–Dec. 1959	Period 2: Jan. 1960–Dec. 1964	Period 3: Jan. 1965–Dec. 1969
Males						
35–39	—	—	—	—	—	—
40–44	—	(8.7)	(14.3)	—	—	(103.5)
45–49	(4.0)	(5.1)	—	—	—	(8.6)
50–54	(5.3)	8.8	(8.8)	—	—	—
55–59	10.5	11.6	8.3	(12.0)	—	—
60–64	17.0	17.3	17.5	11.2	(10.7)	(48.0)
65–69	18.6	29.4	34.3	25.1	16.9	43.5
70–74	32.3	26.4	19.2	39.9	40.5	38.2
75–79	32.7	41.5	58.6	(37.8)	(15.0)	47.2
80–84	(47.9)	106.8	51.9	—	(200.6)	(20.6)
85–89	61.8	152.7	(69.9)	(595.2)	—	—
No. of deaths	52	74	69	38	52	78
Age-standardized death rate	12.5	18.5	15.8	18.9	13.4	19.6
Females						
35–39	—	—	—			
40–44	—	(3.5)	(3.5)			
45–49	5.9	(3.3)	(1.6)			
50–54	5.2	7.7	(3.0)			
55–59	7.4	8.0	5.8			
60–64	14.0	12.3	14.5			
65–69	15.6	15.2	17.7			
70–74	19.4	21.1	22.0			
75–79	37.3	30.5	36.3			
80–84	51.5	45.1	40.8			
85–89	53.4	44.5	59.5			
No. of deaths	175	184	205			
Age-standardized death rate	13.8	12.9	13.1			

[a] Some 5-yr age groups were combined in the standardization of rates to avoid 0 cases in these groups.
[b] *Numbers in parentheses* indicate <5 deaths in group.

year age groups were small and subject to considerable sampling variation. There was no appearance of any consistent increase in the lung cancer death rate among nonsmokers with time by 5-year age groups. The age-standardized rates for males shown in table 1 and in text-figure 1 showed no trend. The rates for women were based on many more cases, and the age-standardized rate was virtually the same in all three periods. The differences in rates between periods 1 and 2 and periods 1 and 3 were not statistically significant in both the ACS study and the Dorn study of veterans. The analysis was based on the underlying cause of death on death certificates. The death rates for the three periods were also standardized to the distribution of the stationary population of white men and women combined, of ages 35 years and over, in the abridged life table for the U.S. population in 1965. This standardization raised the rates for males slightly and decreased the rates for females slightly, but it changed the pattern of the trends very little.

An attempt was made in the first 6 years of follow-up in the ACS study to obtain confirmation of diagnosis for all cases with cancer from physicians who signed the death certificates or from hospitals in which death occurred. Information was received confirming the primary site of cancer in 78% of the cases, and microscopic confirmation was obtained in 69% of the cases in the first 6 years (*6*).

Table 2 shows a comparison of the death certificate diagnosis and the final diagnosis from the medical report. Among nonsmoking men, 74 were reported to have died of lung cancer according to the death certificates. Six of these (8.1%) were reported to have died of cancer of another site on the final report. However, 9 (0.8%) of the deaths reported as being due to cancer of a site other than lung on death certificates proved to be due to lung cancer on the final report. Thus among nonsmoking men there were 74 deaths from lung cancer reported on death certificates and 77 deaths from lung cancer according to the final medical report.



TEXT-FIGURE 1.—Lung cancer mortality rates in three 4-yr periods for nonsmokers in the ACS prospective study and for nonsmokers in three 5-yr periods in the Dorn study of veterans.

TABLE 2.—*Lung cancer deaths among nonsmokers in first 6 years of study on death certificates and on final reports*

Final report diagnosis	Death certificate diagnosis			
	Lung cancer		Other cancer	
	No.	Percent	No.	Percent
Males				
Lung cancer	68	91.9	9	0.8
Other cancer	6	8.1	1,153	99.2
Total	74	100.0	1,162	100.0
Females				
Lung cancer	169	83.3	10	0.2
Other cancer	34	16.7	5,160	99.8
Total	203	100.0	5,170	100.0

In women the picture was somewhat different. Two hundred and three cases of lung cancer among nonsmokers were reported to be lung cancers on death certificates, and 34 (16.7%) were reported to be cancers of other sites on the final medical report. A smaller number, 10 (0.8%), of those cancers that were reported as being of a site other than the lung on death certificates were reported to be lung cancers on the final report. Thus on death certificate reports, 203 nonsmoking women were reported to have died of lung cancer in the first 6 years. On the final report, 179 (a decrease of 11.8%) were reported to have died of lung cancer. About one-third of the 34 females whose causes of death were attributed to lung cancer on the death certificates and changed on medical confirmation died from breast cancers. However, breast cancer was underdiagnosed on death certificates in nonsmoking women. There were 1,310 breast cancers reported on death certificates in the first 6 years of the study and 1,371 on the final report.

Table 3 shows the age-standardized rates for total mortality for all cancers and for cancers of selected sites among nonsmokers in the three time periods. Overall mortality in men decreased 3% from period 1 to 3. This slight difference was statistically significant at the $P<0.05$ level because of the large number of deaths involved. None of the differences in total cancer or in cancers of other sites in men in table 3 between periods 1 and 2 and periods 1 and 3 were statistically significant. Women had an 8% decrease in total death rates between periods 1 and 3. The difference in rates was statistically significant. The decreases in total cancer and uterine cancer between periods 1 and 2 and periods 1 and 3 were statistically significant. None of the differences for cancers of other sites were statistically significant except for the 29% decrease in cancers of the buccal cavity, pharynx, larynx, and esophagus between periods 1 and 3.

Passive Smoking

A number of studies have established that nonsmokers exposed to smoke from cigarettes in a poorly

TABLE 3.—*Trends in mortality rates from cancers of selected sites in three time periods for nonsmokers: ACS prospective study, 1960–7*

Parameter	No. of deaths	Period 1: July 1960–June 1964	Period 2: July 1964–June 1968	Period 3: July 1968–June 1972
Males				
Total deaths	19,805	1,608.7	1,588.6	1,559.9
Total cancers	3,151	247.8	252.4	251.6
Cancers of buccal cavity, pharynx, larynx, and esophagus	62	6.86	6.79	5.46
Cancer of colon–rectum	636	51.9	45.0	50.4
Cancer of pancreas	199	15.0	17.6	14.0
Cancer of prostate gland	573	69.5	63.1	59.6
Females				
Total deaths	52,965	1,494.5	1,485.8	1,374.2
Total cancers	13,275	317.9	304.6	298.1
Cancers of buccal cavity, pharynx, larynx, and esophagus	159	4.88	4.21	3.48
Cancer of colon–rectum	2,429	58.0	59.8	56.7
Cancer of pancreas	688	17.4	16.2	14.8
Cancer of breast	3,186	69.3	68.0	75.0
Cancer of uterus	833	22.1	18.4	15.0

ventilated room will show increased levels of carbon monoxide in their blood. These higher levels of carbon monoxide can result in deterioration of psychomotor performance. Many nonsmokers have acute eye and throat irritation responses in the environment of cigarette smokers (*11*). One paper reported changes in lung function tests in people classified as passive smokers compared to nonsmokers, and these changes were interpreted as demonstrating a greater reduction in the function of small airways (*12*). Hirayama (*13*) reported lung cancer mortality ratios in Japan ranging up to 2:1 in nonsmoking women with husbands who smoked 20 or more cigarettes a day compared to nonsmoking women with nonsmoking husbands. Trichopolous et al. (*14*) reported similar findings in a case-control study in Greece.

A similar analysis was made of nonsmokers in the ACS study, even though classifying nonsmoking women on the basis of the smoking habits of their husbands is not an accurate measure of their degree of passive smoking. Moreover, exposures in Japan and Greece may be very different than they are in the United States. Lung cancer mortality among persons who were married to cigarette smokers was compared with the mortality among those married to nonsmokers.

A total of 176,739 nonsmoking women were identified who were married *a*) to men who never smoked, *b*) to men who currently smoked cigarettes regularly but less than 20 cigarettes a day, and *c*) to men who currently smoked 20 or more cigarettes a day. Most husbands had smoked for 20 or more years before the study began, and presumably their wives were more likely to have been passive smokers than were the women married to nonsmokers. Twenty-eight percent of the husbands of nonsmoking women were nonsmokers compared to 21% of men in the total study population. Table 4 shows the results of this analysis. Expected numbers of deaths were based on the lung cancer rates for the 12-year period (1960–72), by 5-year age groups of the women with nonsmoking husbands. No attempt was made in this first analysis to adjust for other possible confounding factors. The observed versus expected lung cancer mortality ratio for women whose husbands smoked less than 20 cigarettes a day was 1.27; for those whose husbands smoked 20 or more cigarettes a day, it was 1.10. Neither of these differences was statistically significant at $P<0.05$ by the Mantel-Haenszel procedure.

A separate matched-groups analysis was made of the lung cancer deaths among the same 3 groups of women to eliminate the possible effects of potential confounding factors. The women in the 3 groups were matched by age (5-yr age groups), race (white, nonwhite), highest educational status of husband or wife (not a high school graduate, high school graduate, or higher), residence (rural, not rural), and husband occupationally exposed to dust, fumes, or vapors (yes or no). The analysis was restricted to nonsmoking women who were not sick and who had no serious disease at the start of the study. "Adjusted" numbers of deaths for each matched diad were computed, as described in other publications (*15*, *16*). In this pro-

TABLE 4.—*Observed versus expected[a] lung cancer deaths among nonsmoking women with cigarette smoking husbands: ACS study, 1960–72[b]*

Parameter	Husband did not smoke	Husband smoked <20 cigarettes/day	Husband smoked ≥20 cigarettes/day
Observed deaths	65	39	49
Expected deaths	65.00	30.67	44.67
Mortality ratio	1.00	1.27	1.10

[a] Expected deaths are based on the lung cancer rates by 5-yr age groups in women with nonsmoking husbands applied to the person-years of women with smoking husbands.

[b] The 95% confidence limit for women with husbands smoking <20 cigarettes/day was 0.85, 1.89; for women with husbands smoking ≥20 cigarettes/day, it was 0.77, 1.61.

TABLE 5.—*Matched group study: Adjusted[a] lung cancer deaths among women with nonsmoking husbands matched[b] with women with smoking husbands*

Group	No. of adjusted lung cancer deaths	Ratio	P^c
Nonsmoking husband	25.6	1.00	
Husband smoked <20 cigarettes/day	35.0	1.37	NS
Nonsmoking husband	34.5	1.00	
Husband smoked ≥20 cigarettes/day	35.8	1.04	NS

[a] See text for definition of adjusted deaths.
[b] Matched on the basis of *a*) wife's 5-yr age group, *b*) husband's occupational exposure, *c*) highest educational level of husband or wife, *d*) race, *e*) urban–rural residence, and *f*) absence of serious disease at the start of the study.
[c] NS = not significant.

cedure women whose husbands never smoked were compared to women from each of the 2 groups in which the husband smoked cigarettes. The number of lung cancer deaths in each matched diad was adjusted to the proportion of persons for each group and summed over all groups to give an "adjusted" number of lung cancer deaths. Variances were computed for each of the matched groups and summed over all matched groups, and probabilities were computed under the null hypothesis of observing no differences. The results of this analysis are shown in table 5. The ratio of adjusted lung cancer deaths in women whose husbands smoked less than 20 cigarettes a day to those in women whose husbands never smoked was 1.37. The comparable ratio for women whose husbands smoked 20 or more cigarettes a day was 1.04. None of these differences were statistically significant ($P>0.05$).

DISCUSSION

Data from the two prospective studies reported in this paper indicate that the age-adjusted mortality rate for lung cancer in nonsmoking men 35–89 years old was between 12 and 19/100,000 in the 1950's and 1960's. The observed rate for women was about 13/100,000. The rate may actually be about 10% less because lung cancer in nonsmoking women may be over-reported on death certificates. The lung cancer rates shown in table 1 may be slightly different from those shown in other publications because different years, age groups, or methods of standardization were employed.

The rates for male and female nonsmokers by age group in this analysis were in about the same range as that of the 1958 rates for nonsmokers in Haenszel's report of a 10% sample of death certificates in the United States (*17, 18*). The 1966–68 estimates derived by Enstrom from several sources are not directly comparable because of a different classification of nonsmokers ("never smoked cigarettes") (*3*). The male rates in the period 1968–72 are about one-half those reported by Enstrom for active Mormons in 1968–75 (*19*). Enstrom defined active Mormons as a cohort that can be considered "almost entirely as white males who never smoked," and he used this cohort to serve as the nonsmoker lung cancer rates in the 1968–75 period "in lieu of recent national mortality data on nonsmokers." The mortality rates for lung cancer in both male and female nonsmokers by 5-year age groups showed no consistent trends over the period in this study.

Long-term effects of passive smoking are difficult to establish because of the problems in classification. It may be misleading to classify a women as a passive smoker or not on the basis of her husband's smoking habit. Wives of nonsmokers may be more exposed to cigarette smoke of others than wives of cigarette-smoking men; wives of smokers may be very little exposed to the cigarette smoke from their husbands or others. In addition, 13% of the women nonsmokers who died of lung cancer in the ACS study reported that they were previously married, and the classification of their exposure to their husbands' smoking may not be pertinent.

In autopsy studies of cigarette smokers, there was a dose-related spectrum of histologic findings, including basal cell hyperplasia, metaplasia, and cells with atypical nuclei in the mucosa of the tracheobronchial tree that may lead to invasive carcinoma. In contrast, advanced histologic changes in specimens from the tracheobronchial tree, such as lesions with six or more cell rows, lesions having 50% or more cells with atypical nuclei, and carcinoma in situ, were found in less than 0.1% of the slides of nonsmokers (*20*). Since there is such little variation in the appearance of these histologic changes in nonsmokers of different age, sex, and residence, it seems doubtful that those nonsmokers who had been heavily exposed to cigarette smoke from others in their lives could have had many more precursor lesions for the development of lung cancer than nonsmokers not so exposed. Therefore, there is evidence from these studies that passive smoking cannot play more than a very small role in the development of lung cancer.

Mortality ratios for male smokers of less than 10 cigarettes a day compared to those of nonsmokers range from 2 to 1 in Japan to nearly 5 to 1 in the United States. Mortality ratios in women are even lower. It appears unlikely on a biologic basis, therefore, that wives with husbands who smoke 20 or more cigarettes a day can have mortality ratios that approach those of regular cigarette smokers.

To obtain data on passive smoking in nonsmoking women, an epidemiologic study should be specifically designed to measure their exposure as accurately as possible. This is very difficult to do. Neither the Japanese study nor the ACS study was designed to obtain definitive information on passive smoking.

Data for lung cancer risks in occupationally exposed nonsmokers compared to nonexposed nonsmokers are

not very extensive. One study showed an increased risk in heavily exposed asbestos workers on the basis of a small number of cases (*21*).

It would be interesting to continue studies of lung cancer trends in nonsmokers over a long period of time, but the major public health problem in lung cancer is with cigarette smokers. Cigarette smokers who are occupationally exposed to asbestos have a greatly elevated risk compared to the risk among cigarette smokers not so exposed (*21*). Lung cancer rates are rising at an alarming rate in women who smoke cigarettes. Educational efforts should focus on smoking-cessation programs for these groups and particularly on persuading young people not to start. Even if the estimates from this analysis are in error and there was a slight increase in lung cancer trends in nonsmokers, it did not appear to be an important problem in the overall picture for the time period of this study.

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